Abuse Liability of Dissolvable Tobacco Products

Public Comment to Tobacco Products Scientific Advisory Committee

Prepared by

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Abstract

In July 2011, Battelle presented an oral statement to Tobacco Products Scientific Advisory Committee (TPSAC) stating our concerns regarding the relatively untested abuse liability potential of dissolvable tobacco products (DTP). We are pleased to offer to TPSAC this more comprehensive and detailed overview of our concerns and recommendations for assessing the abuse potential of these products. The abuse and addiction potentials of DTP are essentially unknown. Our recommendations are directed toward experimental approaches that employ comparisons of quantitative pharmacokinetic and pharmacodynamic effects and qualitative assessment of the risk perceptions from advertisements and promotional materials across a wide range of doses and in vulnerable populations. Although there have been some preliminary studies on the pharmacology of DTP, the studies were limited by the dose range, the populations tested and the products considered. This overall paucity of information precludes reliable estimates of abuse liability of DTP when they become widely available on the commercial market. This report contains our recommendations for studies that would expand that knowledge base. Specifically, we emphasize the clinical testing of DTP in: adults (male and female) current tobacco users, non users and former users; youth current tobacco users; adults and youth when DTP are tested at higher doses, when taken with food, after tobacco abstinence, and among nontobacco users; and when used as Modified Risk Tobacco Products (MRTP). The data from these proposed studies are needed to place DTP in the continuum of addiction potential among oral and combustible tobacco products and pharmaceutical nicotine products. Such studies will provide science-based assessment of DTP abuse potential and inform regulatory decisions associated with these products.

Background

The 1988 Surgeon General's Report on the Health Consequences of Smoking (US Department of Health and Human Services, 1988) comprehensively reviewed the available scientific literature and concluded the following: that cigarettes and other forms of tobacco are addicting; nicotine is the drug in tobacco that causes addiction and that the pharmacologic and behavioral processes that lead to tobacco addiction are similar to those that determine addiction to other drugs, such as heroin and cocaine. This landmark publication and the official recognition of the addictive nature of tobacco products contributed to the passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) of 2009 allowing for the regulation of tobacco products by the Food and Drug Administration (FDA; FDA, 2011a).

Since the publication of the 1988 Surgeon General's Report there have been major changes in the domestic tobacco market and the domestic use of tobacco products. For example, adult smoking rates have decreased from 28.1% in 1988 to 19.3%, currently (Centers for Disease Control and Prevention [CDC], 1991; CDC, 2011, respectively), and smoking among high school students has decreased from 26.0% to 17.2% in 2009 (US Department of Health and Human Services, 1988; CDC, 2010, respectively). Although cigarette smoking has diminished there has been an increase in concomitant conventional cigar use (Substance Abuse and Mental Health Services Administration, 2007) and an especially large increase in little cigar and cigarillo use (Cullen et al., 2011). In addition, despite a decrease in chewing tobacco use, the use of moist snuff and other oral tobacco products have increased (Federal Trade Commission, 2009). Finally, new products that deliver nicotine but are substantially different from conventional tobacco products, such as e-cigarettes, hookah, Premier, and Snus, have been introduced into the market place and are gaining in popularity.

The DTP are another newly introduced product. The first DTP, Ariva, was introduced by Star Tobacco in 2001. The DTP are compressed tobacco products that dissolve in the mouth making nicotine and other components of tobacco available for buccal absorption. The DTP are usually sweetened and may

be flavored or unflavored. Unlike moist snuff, Snus, and chewing tobacco where the user must expectorate, the DTP user swallows the expectorant—i.e. they are spitless products. This is an important characteristic of the DTP because they are advertised for use by cigarette smokers when they are in situations where smoking (and presumably spitting) is not allowed. Being spitless may also appeal to US women as their use is more easily concealed. Internet advertising and promotion of DTP explicitly and implicitly suggest that women may find the product appealing (Star Scientific, 2007). DTP also appeal to youth who are attracted to their candy-like appearance and who may also wish to conceal tobacco use. These spitless products represent a new initiative by the tobacco industry to popularize the use of oral tobacco in the United States. Oral tobacco is used predominately by men in the US but in the developing world oral tobacco use among women is quite common (International Agency for Research on Cancer [IARC], 2007). Although initial marketing efforts appear to be directed at current smokers, DTP may also appeal to women, pregnant women smokers, youth and former smokers (Romito et al., 2011). However, as seen with other tobacco products introduced into the market and advertised as lower risk (e.g. light cigarettes, filter cigarettes; Institute of Medicine [IOM], 2001), it may be years before the health implications of dissolvable tobacco product use is manifest; therefore, the assertion of lower is risk is premature.

FDA Challenges

Under provisions of the FSPTCA and in subsequent court decisions the FDA has the authority to regulate cigarettes, smokeless tobacco and roll your own tobacco. The FDA intends to propose a regulation that would extend regulatory control to DTP that meet the statutory definition of a tobacco product—DTP would thus become subject to FDA regulations. In a recent document the FDA asserted its jurisdiction over DTP because they are regarded as smokeless tobacco products (FDA, 2011b). Initial public comment and expert testimony has been presented to the FDA TPSAC in July, 2011 (FDA, 2011c). At that meeting, some of the following challenges facing the FDA were reviewed.

No unique statutory definition of DTP

Currently, the FDA has taken the position that DTP meet the statutory definition of a smokeless tobacco product:

> "Any tobacco product that consists of cut ground powdered or leaf tobacco intended to be placed in the oral or nasal cavity".

By establishing a unique legal definition of DTP these products can be regulated independently of regulations imposed on smokeless tobacco products. A separate definition seems appropriate because there are major differences between DTP and smokeless tobacco. For example, DTP are spitless, the juices are typically swallowed and when they "dissolve" no product is left after consumption. Furthermore, the nicotine content in a unit dose of currently marketed DTP (0.6-3.1 mg; Rainey et al., 2011) is generally much lower than the nicotine content of a typical dose of moist snuff of 7-11 mg (IARC, 2007; Henningfield, Radzius & Cone, 1995; Richter et al., 2008). The adoption of a legal definition has implications for the evaluation of the public and personal health risks of the DTP. Restrictions on advertisement, promotional material, availability, marketing and packaging and warning labels contribute to the risk perception and acceptability.

Minimal information available

Most of the information on the DTP is held by their manufacturers; there have been relatively few published reports in the peer-reviewed scientific literature. The lack of peer reviewed literature is understandable since these are relatively new products and they have only small market penetration. At

the July TPSAC meeting, Sarah Evans, Ph.D. of the FDA's Center of Tobacco Products stated that a comprehensive search of the extant scientific literature revealed only 22 peer reviewed articles that addressed various aspects of DTP use (FDA, 2011c; FDA, 2011d). Some studies cited were focus group (O'Hegerty et al., 2007; Parascandola et al., 2009), epidemiologic studies (Slater et al., 2008), biomarker Stepanov et al., 2006) and clinical studies (Blank & Eissenberg 2010; Blank et al., 2008; Kotlyar et al., 2007; Hatsukami et al., 2011). Since the July TPSAC meeting, there was a report (Seidenberg et al., 2011) that RJ Reynolds has introduced DTP, marketed as Revo, available in Orbs, Strips and Sticks in Taiwan; making this the first known foray for DTP into the international tobacco market.

Also in her presentation at the July TPSAC meeting Sarah Evans, Ph.D. stated that DTP manufacturers are required to submit specified data to FDA, while other data is requested but is voluntary. The required information includes marketing research, marketing practices and their effectiveness, health, toxicological, behavioral and physiologic effects of DTP. The voluntary information includes specific information on composition and design, marketing research on the use by age, type of tobacco use, interest in quitting and short summaries on appeal, use, cessation, dual use with cigarettes, abuse liability and chemosensory effects. Much of this voluntary information is relevant for considerations of abuse liability and addiction risk particularly in vulnerable populations. Thus, the DTP producers may have important information for regulatory decisions but it is unclear how much of that will be surrendered, whether the study descriptions and data submitted can be interpreted, and there is no certainty of the content of the information available. It seems apparent that eventually these critical data must come from independent research or from the DTP producers and be independently verified. A significant concern of the former approach is that DTP products are generally only available for independent testing after they have been marketed. We recommend independent testing and/or verification of industry testing of DTP before they are approved for general marketing.

In summary, the FDA is considering how DTP are to be regulated. These products have the potential for both beneficial and detrimental public health consequences. However, agreement seems lacking on what these DTP are and there is little empirical data from independent sources on the abuse liability and toxicity of these products. These challenges complicate the formulation of a rationale basis for regulation. As discussed below there is a need for data from pharmacodynamic and pharmacokinetic studies to define the effects seen after administration of DTP, specific data about their abuse liability, and qualitative data from interviews and focus groups to provide information about use patterns, appeal and risk perception as they related to abuse liability.

Recommendations for the FDA on the Abuse Liability Assessment among DTP

The IOM Report (2011) on MRTP is the most recent of many publications that recognize the complexities of assessing abuse potential among tobacco products (see also: Jasinski et al., 1984; Carter et al., 2009, Jasinski and Henningfield 1989). This IOM Report recognizes that no single measure or experimental design can account for all of the variables that contribute to the reinforcing potential of products that deliver nicotine. Rather the IOM of Medicine Report suggests the importance of abuse liability testing in a broad sample of subjects and specifically points out the importance of abuse liability assessment as a function of: demographics (age, SES, gender), tobacco history (smokers, oral tobacco user, former or never smoker), level of tobacco dependence, usual choice of tobacco product, and intentions of continued tobacco use or cessation.

We regard data from the following three experimental paradigms to be especially important in the assessment of abuse potential.

1. *Conduct Pharmacokinetic/Pharmacodynamic Studies*

Among the most direct assessment of abuse liability from tobacco products is their rate and amount of nicotine delivery (Fant et al., 1997; Fant et al., 1999; Pickworth & Henningfield, 1997). The Surgeon General's Report (US Department of Health and Human Services, 1988) provides comprehensive overwhelming support for the notion that nicotine is the substance in tobacco that drives addiction and its continued use. Thus our first recommendation for abuse liability testing of DTP is for studies to measure the speed and amount of nicotine delivery in human volunteers that utilize a variety of different experimental paradigms. For example, these studies should compare the pharmacokinetic characteristics of all of the marketed and proposed DTP. The pharmacokinetic properties of other smokeless tobacco products (e.g. moist snuff and Snus) and combustible tobacco products should be compared to the DTP in the same paradigm. The pharmacokinetic studies of DTP should have flexibility in dosing since some consumers may use more than one dose at a time. Furthermore, the influence of concomitant ingestion of acidic or alkaline foods and beverages should be assesses because mouth pH is known to affect nicotine absorption from smokeless tobacco (Fant et al., 1999) and from nicotine gum (Henningfield et al., 1990). Both the nicotine content and the dissolution rate differ among DTP. For example, the nicotine content varies between 0.6 mg and 3.1 mg per unit dose and the dissolution rate of a Camel Strip is about 3 min, whereas as a Camel Orb dissolves over 15 min (Rainey et al., 2011). To assess abuse liability of DTP, their rate and amount of nicotine absorption would be compared to other oral tobacco and pharmaceutical nicotine delivery products.

Pharmacokinetic studies are designed to test the acute administration of the standardized or commercial DTP in human volunteers. The design typically includes a within-subject comparison of multiple doses, and includes a referent compound and may include a placebo condition. Pharmacokinetic studies involve multiple blood draws before and at specified times after DTP administration to assess the rate and amount of nicotine absorption, rate of elimination, and overall nicotine exposure. The profiles of the DTP could be compared with other oral nicotine delivery products (e.g. moist snuff, or nicotine gum) and compared to subjective assessments of product strength and liking. Some preliminary research is available to guide the experimental design considerations of future studies. For example, Blank and Eissenberg (2010) compared a DTP (Ariva) to own brand cigarette, Camel Snus and no smoking in a 5 day, within subject, crossover study that measured nicotine, NNAL and CO exposure and subjective estimates. They reported very little increase in plasma nicotine after the DTP but a reduction in tobacco craving. Levels of tobacco specific nitrosamines in DTP (Jensen et al., 2006; Stepanov et al., 2011) and in the urine of DTP users (Mendoza-Baumgart et al., 2007) indicate that the exposure to tobacco carcinogens was generally lower from DTP than from conventional tobacco products. Kotlyar et al. (2007) compared the pharmacokinetic and subjective effects of three DTP (Ariva, Stonewall and Revel) to a popular moist snuff (Copenhagen) and a medicinal nicotine lozenge (Commit). Copenhagen caused significantly larger increases in plasma nicotine than the other products; the Commit lozenge delivered more nicotine than either Ariva or Revel. These studies provide important preliminary assessments of pharmacokinetic and pharmacodynamic activity of a few DTP in highly structured laboratory environments. However, the lower nicotine exposure from DTP should not be regarded as final evidence that DTP have low or no abuse potential.

2. *Assess Subjective Effects Associated with DTP*

The FDA requires an abuse liability assessment of all psychoactive drugs as part of an Investigational New Drug (IND) application. As discussed above, the addiction liability of tobacco products is through the rapid delivery of nicotine (US Department of Health and Human Services, 1988, Fant et al., 1997; Fant et al., 1999; Pickworth & Henningfield, 1997). Pharmaceutical products that deliver nicotine

slowly, (e.g. nicotine patch and gum) are approved for OTC sale (to adults) whereas others that deliver nicotine more rapidly (e.g. nicotine nasal spray or inhalers) are prescription only products. However, all DTP (even those that rapidly dissolve) are available for over-the- counter sales to adults, even though there is little data about the rate of nicotine delivery. Another consideration in measures of abuse liability is their subjective effects. Subjective effects may be assessed by simple questionnaires that index "liking", "appeal", "intentions to use again", "relative value", etc. Such studies have proven invaluable in assessing the reinforcing properties of drugs including nicotine and tobacco products in humans (Henningfield & Jasinski, 1984)

The selection of the appropriate subject population in drug abuse assessment studies is critical (Review: IOM, 2011; Carter et al., 2009). For example, heroin users give very high liking scores to heroin and other opiates, but non opiate users do not like the effects opiates (Martin and Sloan, 1977) just as nonsmokers do not like cigarettes. It is critically important to conduct abuse liability assessments of DTPs in potential consumers of these products—current DTP users, smokeless tobacco users, current smokers, women, etc. These groups will likely give a very different subjective assessment of the products. It is also important to regulate the context in the subjective experiments—the products may reduce tobacco withdrawal (Blank & Eissenberg, 2011) so that their appeal may increase while participants are tobacco abstinent and whereas their appeal may diminish when they are full satiated. Hatsukami et al. (2011) tested product liking of DTP in smokers wishing to use these products to quit smoking. They reported no difference in preferences for four of the five oral tobacco products; however, there was inconsistent use when the participants subsequently used the products for smoking cessation.

Subjective responses to DTP could be conducted in conjunction with pharmacokinetic studies. These studies will provide data to establish the relation between plasma levels of nicotine and the subjective/reinforcing effects after DTP. The range of subjective effects assessed is broad—at a minimum there should be estimates made of product liking, specific effects such as "head rush", "high", "liking", "increased concentration", and items that measure suppression of tobacco abstinence symptoms. Subjective pharmacodynamic effects of DTP should also be established in tobacco abstinent smokers because their appeal may change with increasing levels of tobacco craving. Recent findings justify extending the testing of DTP in women smokers and nonsmokers. The use of DTP by women has already started to grow—nearly 45% of DTP purchases are made by women but women buy less than 15% of smokeless tobacco products (Craver, 2011) and women are a market target in Internet advertisements for DTP use (Star Scientific, 2011). Young adults and older children are another population that may be (with proper protections) assessed for pharmacodynamic effects. Use of DTP in this age group is evident—and the possibility of concealment is a feature that may appeal to youth. Comparisons between traditional oral tobacco (moist snuff) and DTP in young adults will determine if there effects and appeal to this vulnerable demographic segment.

3. *Conduct Qualitative Research*

Qualitative data collected from individuals and in focus groups have proven invaluable in drug abuse research to define subjective evaluations of a product, its appeal, comparisons with other tobacco products, the strength and messaging of its advertisement and promotional material. The experiences, opinions and suggestions of specific consumer groups are critically important in the evaluation of tobacco products. As discussed in the recent IOM of Medicine Report on modified risk tobacco products (MRTP [2011]) the reinforcing value of products change as a function of the population in which they are tested. DTP must be assessed in the population most likely to consume them—e.g. youth, women, current smokers, former smokers, never smokers, current and former moist snuff users.

The appeal of the products, the familiarity with the products, the levels of interest and awareness are all indicators of their eventual market penetration and ultimately the public health consequences. Focus group studies are especially important for new products and the public perception of their health risk, patterns of use, expectations, desirable and undesirable characteristics. These studies inform the design of pharmacodynamic and pharmacokinetic studies because they provide information about dose, frequency of use, concomitant use when smoking, importance for relieving tobacco withdrawal and popular perceptions of DTP as smoking cessation aids.

Collection of qualitative data from children and young adults pose little risk but have large potential benefit by sampling the opinions, perceptions and beliefs of a population that has potential market importance. As other tobacco products are regulated and their accessibility limited, the appeal for DTP may increase in children and young adults. This possibility should be tested in qualitative longitudinal or repeated cross sectional qualitative studies of children and young adults.

Summary

An extensive abuse liability assessment of DTP is needed to protect the public health. Very little data are now available that directly tests the abuse potential of DTP. Such data can be obtained from pharmacokinetic/pharmacodynamic studies that assess the rate and amount of nicotine absorption and availability, the subjective effects of DTP administration and from qualitative data collected in interviews and focus groups. It is important that studies have broad diversity in the populations tested, the doses of DTP used and the subjective measures assessed. We further recommend that objective assessment and testing begin before marketing, and continue after marketing. Many agents of abuse, such as long-acting opiates, dextromethorphan, and certain antihistamines, have unintended and harmful effects that may only be recognized after marketing (IOM, 2011), just as the adverse public health consequences of filtered and light cigarettes took years to manifest (IOM, 2001).

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